

# Topological Characterization of Protein-Protein Interaction via Implementing Large Scale Interaction Networks in Mycobacterium Tuberculosis H37Rv

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## Abstract

This research manuscript essentially emphasizes the retrieval of Mycobacterium Tuberculosis H37Rv SuperTarget proteins to provide STRING Database with network structure. The data acquired were thus further analyzed for the aforementioned organism's protein-protein interaction network, eventually resulting in network model construction via Cytoscape 3.1.1. The relations between the entities that constitute a system are mainly revealed by a network model. Henceforth, these results help to research the intricacies of complex systems in different disciplines, including social science, computer science, and life sciences. Biological roles that are a result of molecular activity in a biological system. They form molecular complexes, modules or pathways that result in a biological function being made as a specialty. Nodes (or vertices) often represent proteins, genes, or metabolites in a biological network, while edges also represent relationships such as controlling physical interactions or gene expression. The basic paradigm of a majority of molecular-level cellular events, transduction and transcription regulation, has been accredited to protein-protein interactions, including signaling. A comprehensive understanding of macromolecular interaction includes a thorough analysis of the interactions between proteins to provide the basics of biological systems, Studied through a number of high-throughput experiments and predicted through a range of computational methods involving a multitude of generated sequence data. This research paper focuses primarily on important computational methods for predicting functional interactions between proteins. It also discusses some of the repositories and resources that play an important role in the studies.

## Article History

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## I. Introduction:

Mycobacterium tuberculosis, causative specialist of tuberculosis has a remarkable, flexible covering on its phone surface (principally because of the nearness of mycolic corrosive), which makes the phones impenetrable to Gram recoloring. The corrosive quick stain is utilized by Ziehl-Neelsen recolor. The physiology of *M. tuberculosis*

requires significant levels of oxygen, basically a pathogen of the mammalian respiratory framework, has its pneumonic sufferings. The most routinely utilized demonstrative strategies for tuberculosis are the tuberculin skin test, corrosive quick stain, and chest radiographs. Late advances in cell mycobacteriology have shown that *M. tuberculosis* utilizes an eminent complex

technique to clasp macrophage work, so as to balance the antimicrobial systems of the intrinsic and versatile insusceptible reactions, in this way accomplishing invulnerable departure. Meta-investigation can comprehensively and restrictively inspect various autonomous information concerning a similar malady, extraordinarily improving the measurable importance and believability of the quality articulation information examination performed.(Yu – Wei Zhang et.al 2019). H. sapiens - M. tuberculosis H37Rv protein-protein collaboration (PPI) information arrangements an imperative device for catching the torment system of the pathogen M. tuberculosis H37Rv. Computational figure is a significant technique to fill the hole in exploratory H. sapiens-M. tuberculosis H37Rv PPI information. Homology-based gauge is generally utilized in anticipating both intra-species and between species PPIs. Nonetheless, a few limitations are not appropriately explained in a few gave works that gauge eukaryote-prokaryote between species PPIs utilizing intra-species layout PPIs. (Hufeng Zhou et.al 2014). Different computational strategies were utilized to perceive sedate focuses for the most watched strain of TB, Mycobacterium tuberculosis H37Rv. (Yeh et.al 2012). Rundown of proteins were distinguished as potential medication focuses of Mycobacterium tuberculosis H37Rv through system centrality examination on protein-protein collaboration system of the pathogen (Melak et.al 2014). a while later, cross-talks between these parts have been look at to identify conceivable quality administrative occasions just as HPIs which are probably going to drive metabolic changes during pathogen's adjustment to the intra-have hypoxic environment.(Tugadri et.al 2018). Different calculations are utilized to help such medication repurposing, yet exceptionally solid strategies consolidate impersonations of intracellular systems and AI are as of now inaccessible. Protein-protein connection systems embroils

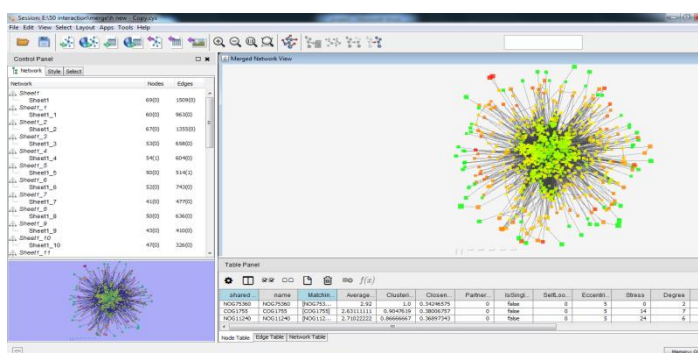
calculation that copy sedate consequences for the information stream. Bolster vector machine to perceive possibly strong medications in our model sickness, psoriasis. Utilizing these techniques 51 medications have been perceived that are possibly viable, and chose three of them for exploratory affirmation. All medications restrained tumor rot factor alpha-induced atomic factor kappa B movement in vitro, recommending they may be powerful for treating psoriasis in people. These medications fundamentally hindered imiquimod-induced ear thickening and aggravation in the mouse model of the illness. All outcomes recommend high expectation execution for the calculation. ( Manczinger et.al 2018). . This article modernizes our research facility's precise investigation of antigens utilizing bioinformatics device to explain the Mycobacterium tuberculosis H37Rv Rv3632 protein's topology and site. (Christian et al 2019). A fundamental essential for any frameworks level comprehension of cell capacities is to accurately reveal and explain every single useful cooperation among proteins in the cell. Here, we present a report on the online database asset Search Tool for the Retrieval of Interacting Genes (STRING); it gives interestingly far reaching inclusion and straightforward entry to both trial just as anticipated communication data. Collaborations in STRING are given a certainty score, and extra data, for example, protein areas and 3D structures is made accessible, all inside a steady and predictable identifier space. New attributes in STRING incorporate an intuitive system watcher that can bunch organizes on request, refreshed on-screen reviews of auxiliary data including homology models, broad information refreshes and unequivocally improved availability and reconciliation with outsider assets. Variant 9.0 of STRING covers in excess of 1100 totally sequenced life forms.

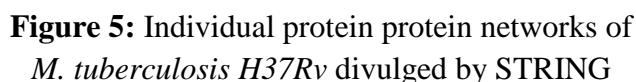
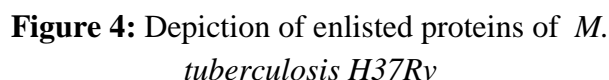
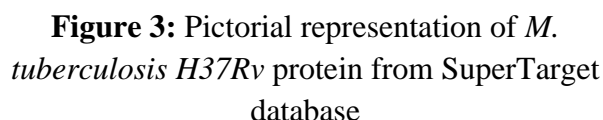
## II. Protein –protein interaction network investigation:

There are different strategies to research the protein-protein communications, for example, High throughput recognition strategy which incorporates yeast two half and half screening and liking mass spectrometry. The natural database has been made where these communications are gathered and protected together for further examination like STRING, DIP (Database of Interacting Protein) and so forth. In a Graphical portrayal, a hub relates to a protein and two proteins have an edge in the event that they physically interface.

### III. Cytoscape 3.1.1:

Cytoscape is a task committed to building open-source arrange perception and examination programming. Programming "Center" gives essential usefulness to format and question the system and to outwardly coordinate the system with state information. The Core is extensible through a module engineering, permitting fast improvement of extra computational investigations and highlights. Cytoscape's underlying foundations are in Systems Biology, where it is utilized for coordinating bimolecular collaboration systems with high-throughput articulation information and other sub-atomic state data. Cytoscape is most dominant when utilized related to huge databases of protein-protein, protein-DNA, and hereditary associations that are progressively accessible for people and model living beings.





Requirements	Small Network Visualization	Large Network Analysis/Visualization
Processor	1GHz	As quick as could be allowed
Memory	512MB	>2GB
Graphics Card	On board Video	Hig hend Graphics Card
Monitor	XGA (1024X768)	Monitor (Wide or Dual)

Table 1: Tabulation of system requirements

Establishment of Java: Downloaded and introduced Java SE 6. Cytoscape 3.1.1 is perfect with Java SE 5 or 6.

Establishment of Cytoscape: There are various choices for downloading and introducing Cytoscape. All choices can be downloaded from the <http://cytoscape.org> site.

**Application Launch:** Double-tapped on the symbol made by the installer. It could likewise be gone through `cytoscape.sh` from the direction line (Linux or Mac OS X) or by means of double tapping `cytoscape.bat` (Windows).

Determination of information record: By picking one of the accompanying choices, contingent upon the document to be opened:

- Option An: Open a Cytoscape session record (.cys)
  - i. Go to File → Open.
  - ii. Select the session record and snap Open.

### Alternative B: Open a content or Excel document

- iii. Go to File → Import... → Network from Table (Text/MS Excel).



iv. A new screen will create the impression that enables you to characterize every datum segment in your document. Pick the record utilizing the Select File button, and a review of the document substance will show up as a guide at the base of the screen.

v. Use the dropdown records gave to characterize the suitable segments containing Source Nodes (purple), Interaction/Edge Type, (red), and Target Nodes (orange). The sneak peaks will shading code every segment likewise; blue is utilized to show segments that will be characterized as edge characteristics. Hub qualities must be imported independently. In the event that you have segments that you don't wish to stack, you can debilitate them by tapping on the header ("Column X") in the review.

vi. Edge properties can be sub delimited inside a segment by right-tapping on the segment header and choosing the List choice as the Attribute Data Type. Choose or enter the suitable List Delimiter and snap OK. Note that this sub delimiter must be not quite the same as the delimiter used to isolate segments.

vii. Troubleshooting: If Cytoscape isn't parsing your content document accurately, you may need to change the propelled settings. Check the container stamped Show Text File Import Options to show these settings. A Reload button is given to invigorate the review once changes are made.

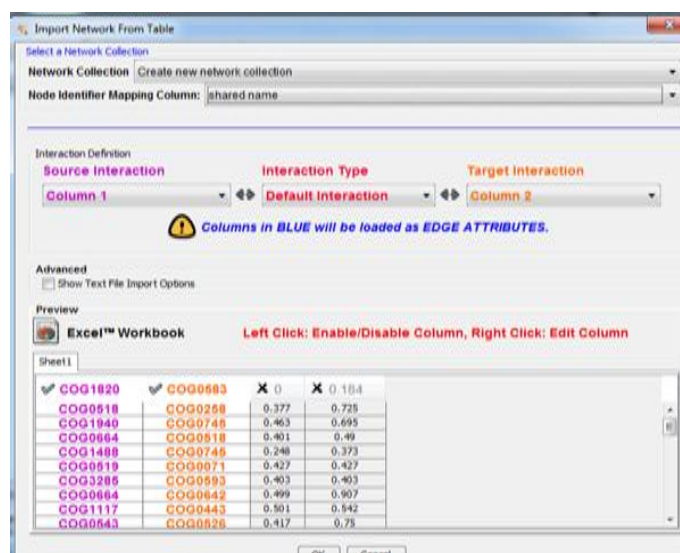
☐ Text is isolated into segments inaccurately: Check which delimiter(s) is/are being utilized. The default settings are Tab and Space.

☐ The first lines of the record ought not be imported: Skip undesirable line(s) by changing the Start Import Row an incentive to the main line number of pertinent information.

☐ The first imported line of the document contains segment names: Check the container stamped Transfer first line as credit names to

change the nonexclusive section names to those in the record.

- The document contains remark lines: Type the proper characters in the Comment Line field to avoid all lines beginning with this string.
- The document contains various segments of target hubs: This is definitely not a legitimate content record design. Have a go at changing over your document to the .sif design or an Excel spreadsheet
- For Excel clients: Only single-sheet exercise manuals are at present upheld.
- Typed H37Rv Mycobacterium tuberculosis naming new system.
- Selected Layout → Files → Organic.



**Figure 6:** Illustration of file being imported from excel spreadsheet containing protein codes

## VI. Sparing Your Network

**Stage 1:** Save your system utilizing the Save or Save as... choices in the File menu. This spares your system as a Cytoscape-explicit .cys record, which you would then be able to open for further review or altering sometime in the not too distant future. You can likewise share these Cytoscape session documents with associates, enabling them to utilize the system too.

**Stage 2:** You can send out your system as a picture utilizing File → Export → Network As

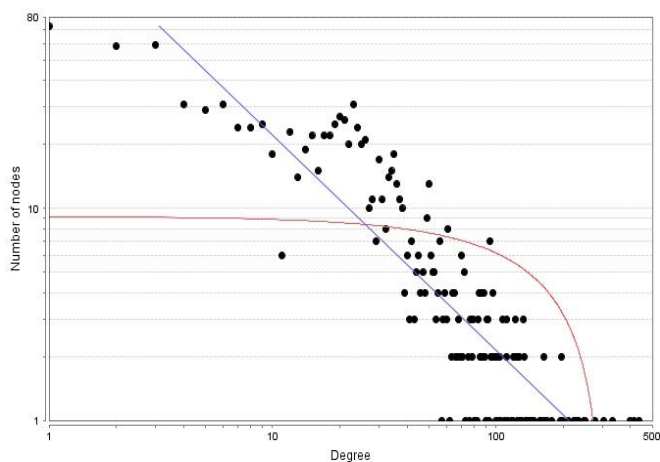
Graphics. Different choices accessible incorporate trading your system as a collaboration information record for use in other programming bundles.

**Stage 3:** Exit Cytoscape by choosing File → Quit.

## VII. Results and Discussions:

In-silico appraisal of the protein-protein associations made through Cytoscape 3.1.1 so as to uncover the similitudes and dissimilarities among the group of proteins enveloped by *Mycobacterium tuberculosis* H37Rv by choosing system topology parameters. On executing the gained information through different databases by means of Cytoscape 3.1.1, these parameters help make organize models.

**Degree dispersion:** In undirected systems, the hub level of a hub  $n$  is the quantity of edges connected to  $n$ . A self-circle of a hub is tallied like two edges for the hub degree. The hub degree dissemination gives the quantity of hubs with degree  $k$  for  $k = 0, 1, \dots$ . In coordinated systems, the in-level of a hub  $n$  is the quantity of approaching edges and the out-degree is the quantity of active edges. Like undirected systems, there are an in-degree appropriation and an out-degree circulation.



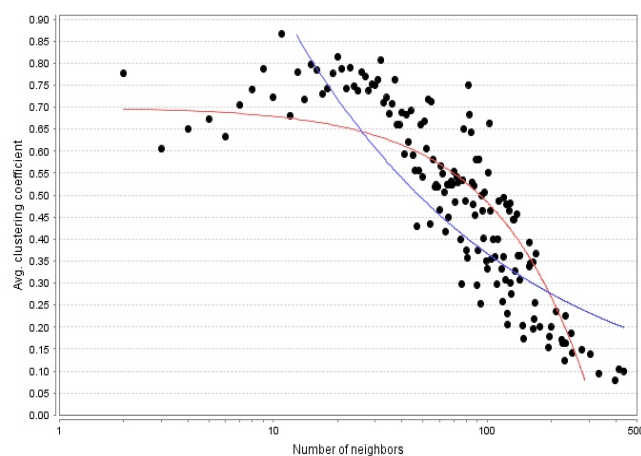
**Figure 7:** Node degree distribution of protein interaction network *Mycobacterium tuberculosis* H37Rv.

The figure displays the decreasing order of node degree distribution of protein. A high degree value

indicates that proteins are highly interactive. The nodes (protein) are serving as alternative checkpoint of clustered proteins which are causative agent of pathogenesis. Protein-protein interaction map would assist in the formulation of novel drug designing stratagem to cure the disease by employing multiple node directed drug designing regime. Note that their degree distributions follow the power law, indicating that they are all scale-free networks

## VIII. Clustering coefficients:

In undirected networks, The average clustering coefficient distribution gives the average of the clustering coefficients for all nodes  $n$  with  $k$  neighbors for  $k = 2$ . The clustering coefficient  $C_n$  of a node  $n$  is defined as  $C_n = (2e_n) / (k_n (k_n - 1))$ , where  $k_n$  is the number of neighbours of  $n$  and  $e_n$  is the number of connected pairs between all neighbors of  $n$ . In directed networks, the definition is slightly different.  $C_n = e_n / (k_n (k_n - 1))$ . In both cases, the clustering coefficient is a ratio  $N/M$ , where  $N$  is the number of edges between the neighbours of  $n$ , and  $M$  is the maximum number of edges that could possibly exist between the neighbours of  $n$ .



**Figure 8:** Representation of average clustering coefficient of network *Mycobacterium tuberculosis* H37Rv

S.NO.	NAME OF THE PROTEIN	CLUSTERING COEFFICIENT
1.	flhB, C694_01470, trxB, rpsL, rpmA, C694_02385, gmk, dnaG, C694_03025, HP_0041, C694_01320, C694_02345, C694_02230,	1.0
2.	CagQ	0.96703297
3.	flgI	0.96428571
4.	Cag4	0.90909091
5.	HP0525	0.8974359
6.	C694_01460	0.89285714
7.	C694_00090	0.86666667
8.	hslU	0.83333333
9.	cagN	0.80632411
10.	C694_03865, C694_03185	0.8

Table 2: Tabulation of proteins & their respective clustering coefficients *Mycobacterium tuberculosis H37Rv*

The clustering coefficient of a node is continually a quantity between 0 and 1. All proteins interacting with the other proteins having a clustering coefficient must be extra than or equal to 1.0. Hence the aforementioned tabulation encompasses all those proteins who have greater diploma of interplay forming a cluster.

S.NO	NAME OF THE PROTEIN	CLUSTERING COEFFICIENT
1.	rlmH, HP_1400, tonB, C694_03540, C694_04710, exbD, HP_0807, exbB, nixA, nikR, C694_03470, C694_05300, C694_07550, rocF, C694_05240, C694_01115, C694_4300,	0.0

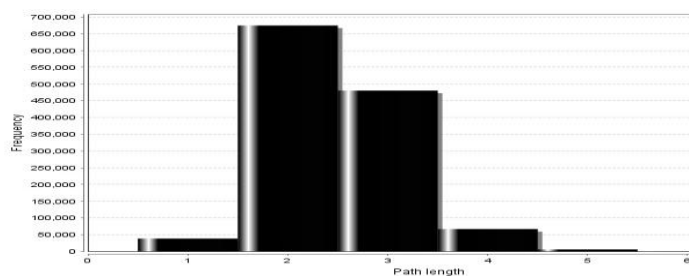
	C694_04910, C694_02070, lpxE, C694_03395, moaE, HP_0232, C694_02165, C694_01765, HP_0496, C694_03795, C694_03760, rpsU, leuS	
2.	aroC	0.04761905
3.	secG	0.05666667
4.	hcpC	0.06410256
5.	rpoB	0.08090118
6.	secF	0.08791209
7.	HP0870	0.1
8.	nadD	0.11538462
9.	fliW2	0.13684211
10.	ahpC	0.14035088

Table 3: Clustering coefficient of Protein-protein interaction in *Mycobacterium tuberculosis H37Rv*

The clustering coefficient of a node is the wide variety of triangles (3-loops) that skip via this node, relative to the maximum range of 3-loops that ought to pass by via the node. All these proteins having a clustering coefficient fee of 0 do now not have interaction with every other at all.

### IX. Shortest paths:

The size of the shortest path between two nodes n and m is  $L(n,m)$ . The shortest route size distribution gives the number of node pairs (n,m) with  $L(n,m) = k$  for  $k = 1, 2, \dots$ . The network diameter is the most size of shortest paths between two nodes. If a community is disconnected, its diameter is the most of all diameters of its linked components. The community diameter and the shortest direction length distribution may additionally indicate small-world residences of the analyzed community.



**Figure 9:** Shortest path length distribution of network *Mycobacterium tuberculosis H37Rv*

The intricacies of two network theory, accompanied through a discussion of the parameters commonly used in analyzing, big net topologies, techniques & networks to discover essential community components, primarily based on perturbations have additionally been described.

S.NO.	NAME OF THE PROTEIN	SHORTEST PATH LEN
1.	C694_06960, HP_0837, C694_02140, C694_04010	3.63819095
2.	lysA	3.48743719
3.	HP_1400, tonB, C694_03540, C694_04710, exbD, HP_0807, exbB, nixA, nikR	3.47738693
4.	HP_0412	3.4120603
5.	C694_02165, C694_01765, leuS, C694_07290	3.40703518
6.	C694_01470	3.39698492
7.	moaE, C694_03795, rpsU	3.39698492
8.	lspA	3.35678392
9.	HP_0232	3.32663317
10.	flhB	3.26633166

**Table 4:** Representation of clustered proteins & estimated path length of *Mycobacterium tuberculosis H37Rv*

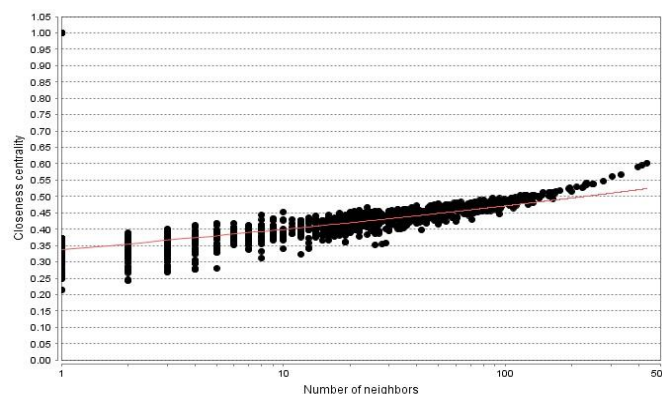
The distributions frequencies of the proteins in particular advocate inter nodal distance. High course size is indicative of the truth that a disturbance (anomaly or pathogenesis) in any protein will have an effect on different protein too. Information arising on one node will leverage different nodes.

Closeness centrality: The closeness centrality  $C_c$

(n) of a node n is described as the reciprocal of the average shortest course length and is computed as follows:  

$$C_c(n) = 1 / \text{avg}(L(n,m))$$
 Where  $L(n,m)$  is the length of the shortest route between two nodes n and m. The closeness centrality of every node is a number between zero and 1. Closeness centrality is a measure of how quickly data spreads from a given node to other reachable nodes in the network.

The more central a node is the lower its total distance from all different nodes. Deciphered from under stated tabulation proteins like ureA, kata, rpoB, and others have a high closeness centrality.



**Figure 10:** Closeness centrality of network *Mycobacterium tuberculosis H37Rv*

S.NO	NAME OF THE PROTEIN	CLOSENESS CENTRALITY
1.	UreA	0.54371585
2.	KatA	0.52230971
3.	rpoB	0.52094241
4.	ahpC	0.49502488
5.	Cag7	0.49135802
6.	groL	0.48536585
7.	groS	0.48184019
8.	recA	0.47380952
9.	secA	0.47268409
10.	dnaK	0.47044917

**Table 5:** Representation of closeness centrality of selected proteins of *Mycobacterium tuberculosis H37Rv*



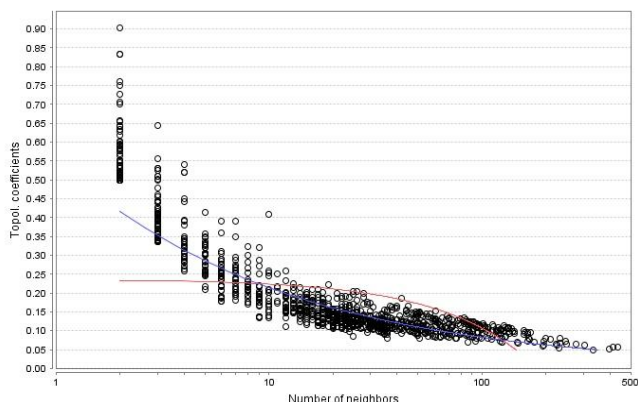
**Topological coefficient:** The topological coefficient  $T_n$  of a node  $n$  with  $k_n$  neighbors is computed as follows:

$$T_n = \text{avg} ( J(n,m) ) / k_n.$$

Here,  $J(n,m)$  is defined for all nodes  $m$  that share at least one neighbor with  $n$ . The value  $J(n,m)$  is the number of neighbors shared between the nodes  $n$  and  $m$ , plus one if there is a direct link between  $n$  and  $m$ .

For example,  $J(b,c) = J(b,d) = J(b,e) = 2$ .

Therefore,  $T_b = 2 / 3$ .



**Figure 11:** Topological coefficient of network Mycobacterium tuberculosis H37Rv

The topological coefficient is a relative measure for the extent to which a node shares neighbors with different nodes. Network Analyzer computes the topological coefficients for all nodes with more than one neighbor in the network. Nodes that have one or no neighbors are assigned a topological coefficient of zero (zero). The chart of the topological coefficients can be used to estimate the tendency of the nodes in the community to have shared neighbors

.Network Parameters	MN(undirected)	MN(directed)
No. of nodes	1140	1140
No. of edges	8288	8288
Avg. shortest path	1266764 (97%)	447661(34%)
No. of hubs	414	414
Avg. clustering	0.625	0.312

coefficient		
Diameter	6	2
Connected component	8	8
Radius	3	1
Characteristic path length	2.470	2.539
Avg. no of neighbors	33.665	33.665
Network density	0.030	0.00
Network heterogeneity	1.328	1.231
Isolated nodes	0	0
No of self loops	0	0
Multi edge node pair	0	0
Analysis time (sec)	136.065	31.645

**Table 6:** Summary tabulation of topological properties of Mycobacterium Tuberculosis H37Rv Protein-Protein interaction networks

Table 6 summarizes the findings of network topology parameters of protein-protein interactions of Mycobacterium tuberculosis H37Rv that were evaluated at some stage in in-silico assessment.

Hubs: In a scale-free network, small-degree nodes are the most abundant, however the frequency of high-degree nodes decreases surprisingly slowly. Thus, nodes that have degrees a great deal greater than average, so-called hubs exist .

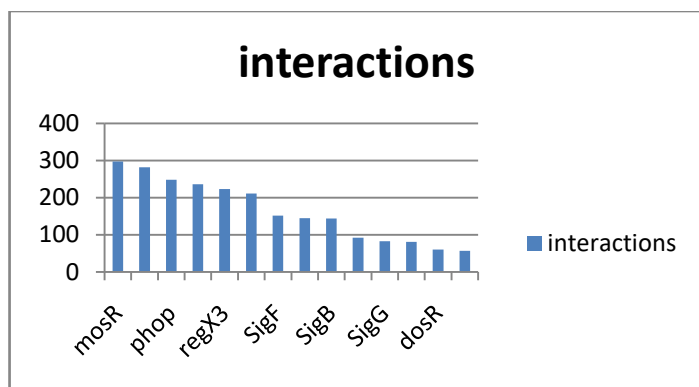


**Figure 12:** Major protein hubs of Mycobacterium tuberculosis H37Rv

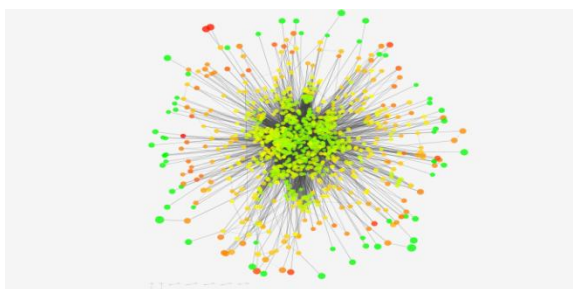
Because of the heterogeneity of scale-free networks, random node disruptions do now not lead to a primary loss of connectivity, but the loss of the hubs causes the breakdown of the community into isolated clusters

## IX. Characterization of Hubs:

Hubs are being characterized particularly on the basis of the proteins having greater diploma of interplay among them. Figure 10 elucidates that *mosR* is the most interactive amongst its neighbors indicating the degree of similarities with which they are correlated. These similarities would serve to establish receptor based drug focused on & therefore subduing pathogenicity.



**Figure 13:** Hubs are characterized depending on the exhibited interactions of various proteins



**Figure 14:** Depiction of protein-protein interaction network in *Mycobacterium tuberculosis* H37Rv. Few highly connected nodes (hubs) holding the network together. The color of a node indicates the phenotypic effect derived from removal of the corresponding protein 1.red: lethal, 2.green: non-lethal, 3.orange: slow growth, 4.yellow: unknown Lethality of crimson colored nodes reveals the pathogenicity of the protein clusters & their damaging interactions for the

hosts.

## Summary & Conclusion:

PPI networks furnish a simplified overview of the web of interactions that take vicinity inside a cell. The enormous amounts of sequence data that have been generated have been leveraged to make higher predictions of interactions and functional associations between proteins, as well as character protein functions. The cutting-edge in-silico study investigates three components viz. host-pathogen interactions (HPIs) between *M. tuberculosis* proteins and human, gene regulatory network challenge to change of *M. tuberculosis* to hypoxia & modification in *M. tuberculosis* metabolism under hypoxic environment. By integrating experimental techniques for determining PPIs and computational strategies for prediction, a lot of beneficial facts on PPIs have been generated, including a number of excessive satisfactory databases. Cytoscape allows the visible integration of the community with expression profiles, phenotypes, and other molecular nation information, and links the network to data bases of practical annotations.

Modern genomic analysis regularly requires workflows incorporating more than one best-of-breed tools. This paper provides the layout and operation of the Cytoscape, which accomplishes this integration, thereby providing crucial evaluation and visualization functionality for GenomeSpace users. The facts received submit in-silico analyses are counseled to go thru in-vitro & in-vivo validations leading to instead substantiated results.

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